REMARKS

With entry of this amendment, claims 24, 26-29, 31-44 and 49-52 are pending in the application. By this amendment, claims 31, 35, 39, 42 and 49 have been amended for clarity, without prejudice. Claims 1-23, 25, 30, 45-48 and 53-56 were previously canceled without prejudice and Applicants continue to reserve the right to pursue the subject matter of these canceled claims in one or more related applications. All of the amendments herein are fully supported by the disclosure, and no new matter has been added to the application.

Impropriety of Final Rejection

As a preliminary matter, it is clear that the present Office Action has been improperly designated as final. In making this determination, the Examiner has stated:

> This is a duplicate of applicant's earlier Application No. 10/764,371. All claims are drawn to the same invention claimed in the earlier application and have been finally rejected on the grounds and art of record in this Office action. Therefore, **THIS ACTION IS MADE FINAL** even though it is a first action in this case (citation omitted). [Office Action, page 7]

This statement is simply not correct. The claims of Application No. 10/764,371 are directed to methods of treating addictive disorders while the claims of the present application are directed to methods of treating different diseases and conditions, that is, attention deficit disorder, depression, obesity, Parkinson's disease, and tic disorders. The claims of the present application are therefore not directed to the same invention as the claims of Application No. 10/764,371. It is clear on this basis that the claims of the instant application have *not* previously been examined, and that the finality of the present Office Action should be withdrawn.

Patentability Under 35 USC § 112, First Paragraph

Claims 24, 26-29, 31-44 and 49-52 have been rejected under 35 USC § 112, first paragraph for alleged failure to comply with the written description requirement (Office Action, pages 2-3). In making this rejection, the Office states that while "[t]he claims are drawn to treating or preventing many disorders (claims 24, 26-29) arising through any mechanism, claims 31-44, 49-52...the specification disclosure is limited to addictive disorder arising from inhibition of dopamine reuptake." (Office Action, page 2) The Office further

asserts that "[t]he diseases listed in the claims are deemed speculations because they are not supported by biological assays or journal articles." (Office Action, page 2)

Claims 24, 26-29, 31-44 and 49-52 are also rejected under 35 USC § 112, first paragraph for alleged lack of enablement (Office Action, pages 3-5). In making this rejection, the Office states:

> [T]he specification, while being enabled for inhibition of dopamine reuptake, does not reasonably provide enablement for all the various mechanisms giving rise to the individual diseases listed in claims 31-44, 49-52, nor does it provide enablement for treating or preventing the diseases listed in claims 24, 26-29. The diseases are deemed speculations because they are not supported by biological assays or journal articles.... [Office Action, pages 3-4]

Applicants respectfully traverse the foregoing grounds of rejection set forth at pp. 2-5 of the Office Action, and submit that the disclosure fully describes and enables the subject matter of original claims 24, 26-29, 31-44 and 49-52.

First, it is not correct, as stated by the Office, that "the specification disclosure is limited to addictive disorder...." (Office Action, page 2) Rather, the specification discloses and enables treatment of a number of diseases and conditions in addition to addictive disorders, including attention-deficit disorder, depression, obesity, Parkinson's disease and tic disorders. (See, for example, Specification, page 9, paragraph [0038] to page 12, paragraph [0054]) Applicants also dispute the contention of the Office that prevention and treatment of these diseases and conditions according to Applicants' disclosure is "speculative." As noted in the specification, each of the diseases set forth in the claims are associated with dopamine disorders. It is specifically described in Applicant's disclosure that Parkinson's disease (Specification, pages 1-2, paragraph [0004]), depression (Specification, page 2, paragraph [0006]), obesity (Specification, pages 2-3, paragraph [0007]; page 4, paragraph [0010]), tic disorders (Specification, page 4, paragraph [0010]) and attention deficit disorder (Specification, page 4, paragraph [0010]) are associated with dopamine disorders. Therefore, it is not speculative that (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane can be effectively employed to treat the subject disorders, which are all described as amenable to treatment by inhibition of dopamine reuptake. In addition, contrary to the assertion of the Office that there are no supporting journal articles, the specification refers to several published journal articles teaching that "successful inhibition of dopamine reuptake has been associated with the treatment of attention deficit disorder, depression, obesity, Parkinson's disease, a tic disorder and an addictive disorder." (Specification, page 24, paragraph [0096]) In addition,

the specification contains detailed, enabling support regarding how the compounds of the present invention are made and used to treat the various diseases and conditions set forth in the claims. For example, the specification contains great detail regarding the preparation (Specification, pages 7-8, paragraphs [0033]-[0035]), use (Specification, pages 8-12, paragraphs [0036]-[0054]), administration (including dosages), and formulation (Specification, pages 12-17, paragraphs [0055]-[0076]) of (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane and pharmaceutically acceptable salts thereof.

Furthermore, Applicants submit that the specification provides descriptive and enabling support for methods to treat and prevent various diseases and conditions using (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane or pharmaceutically acceptable salts thereof, irrespective of the exact mechanism of action of this compound, and dispute any contention to the contrary. Nonetheless, independent claims 31, 35, 39, 42 and 49, and by extension all claims dependent on these claims, have been amended to clarify that the subject diseases and conditions are "alleviated by inhibiting dopamine reuptake". These amendments are presented for clarity and to advance certain aspects of the invention to issuance. Any subject matter withdrawn from prosecution by these amendments is withdrawn without prejudice, and Applicants reserve the right to pursue all additional subject matter supported by the disclosure in one or more related applications.

The Office suggests that deleting the word "prevention" from the claims will, in part, overcome the rejection of the claims for lack of enablement. This is not believed necessary to substantiate enablement of the subject technology. Prevention is defined in the specification as referring "to a reduction in the risk of acquiring a disorder alleviated by inhibiting dopamine reuptake or to the reduction of the risk of recurrence of the disorder once cured or restored to a normal state." (Specification, page 9, paragraph [0037]) In many instances (eg., depression), an individual needs to continue to take a drug in order to prevent a recurrence of the condition being treated. Applicants are therefore entitled to the full scope of their invention, including claims directed to the "prevention" of the various diseases and conditions set forth in the claims.

Finally, the Office's reasoning is not clear to Applicants with respect to the discussion of incorporation by reference on page 3 of the Office Action (relating to references discussed in the last paragraph of page 3 of the specification). The cited journal articles appear to refer to various ways to treat addictive disorders and are therefore not directly pertinent to the claims presently under consideration.

For the foregoing reasons, the rejections of claims 24, 26-29, 31-44 and 49-52 under 35 USC § 112, first paragraph for failure to comply with the written description requirement and failure to comply with the enablement requirement are respectfully submitted to be overcome.

Patentability Under 35 USC § 112, Second Paragraph

Claims 24, 26-29, 31-44 and 49-52 have been rejected under 35 U.S.C. 112, second paragraph as allegedly indefinite for cited by the Office in support of the above-noted rejections under 35 U.S.C. 112, first paragraph. For the reasons discussed above, this rejection is also believed to be overcome.

The Office also levies a rejection under 35 USC § 112, second paragraph, on the ground that that claim 38 is allegedly a duplicate of claim 27, and claim 52 is allegedly a duplicate of claim 29. These rejections are respectfully submitted to be improper, because claim 27 and claim 38 are dependent on claims of clearly different scope (claim 24 and claim 35, respectively). Similarly, claim 29 and 52 are dependent on claims of different scope (claim 21 and claim 49, respectively). Therefore, Applicants respectfully request that these rejections be withdrawn.

Patentability Under 35 USC § 103

Claims 22, 26-29, 31-44 and 49-52 are rejected under 35 USC § 103(a) as allegedly unpatentable over Beer et al., US 6,204,284 B1, for reasons of record.

Applicants respectfully traverse the asserted grounds of rejection and submit that the subject matter of claims 22, 26-29, 31-44 and 49-52 is neither disclosed nor suggested by Beer et al., US 6,204,284 B1.

Beer et al. is generally directed to the treatment of addictive disorders such as chemical substance abuse using the racemic mixture of 1-(3, 4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane. There is no disclosure or suggestion in Beer et al. that the racemic mixture of Beer et al., nor the compounds of the present invention, can be effectively used in the treatment or prevention of attention-deficit disorder, depression, Parkinson's disease and/or tic disorders

In presenting this rejection, the Office minimizes the differences between the racemic mixture of Beer et al. and the compounds of the present invention which are substantially free of the (+) enantiomer. Although the Office asserts that the (-) isomer of the present invention and the racemic mixture of Beer et al. "have both isomers except in degrees," there is no

evidence provided by the Office regarding how much of each isomer is contained in the racemic mixture of Beer et al. On the other hand, the specification indicates that "[t]he term "substantially free of its corresponding (+) enantiomer means containing no more than about 5% w/w of the corresponding (+) enantiomer." (Specification, p.6, paragraph [0029]) It is also clear from the specification that the (-) isomer of the present invention has substantially and unexpectedly different biological properties as compared to the racemic mixture of Beer et al. In particular, the data in Table 1 on page 23 of the specification shows that while both the racemic mixture and (-) isomer have affinity for the dopamine reuptake site of the dopamine transporter, the racemic mixture actually has a *higher* binding affinity for this site than the (-) isomer, that is, the (-) isomer is not *more* reactive, but is in fact *less* reactive, than the racemic mixture. Furthermore, the data in Tables 2 and 3 on page 23 of the specification indicates that the racemic mixture has affinity for the norepinephrine uptake site of the norepinephrine transporter and the serotonin uptake site of the serotonin transporter, while the (-) isomer exhibited no measurable affinity for these sites.

It should be noted that Beer et al. repeatedly asserts that inhibition of the uptake of 5-hydroxytrptamine, norepinephrine *AND* dopamine is needed for effective treatment of addictive disorders. For example:

> It has also been found that 1-substituted--(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexanes can inhibit the uptake of 5-hydroxytrptamine (5-HT), norepinephrine (NE) and dopamine (DA) in crude rat brain synaptosomal preparations, and may be useful, therefore, as agents for the treatment and relief of addictive disorders such as chemical substance abuse, eating disorders resulting in anorexia or obesity and other compulsive disorders. [Beer et al., column 2, lines 18-26]

It is also asserted in Beer et al. that 1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane is a selective 5-HT reuptake inhibitor. In particular:

> The results of this experiment show that 1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, *a selective 5-HT inhibitor*, does provide an attenuation in ethanol consumption in rats. [Beer et al., column 5, lines 49-52, emphasis added]

There is no indication or suggestion in Beer et al. that an isolated (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, which Applicants have shown to have no measurable affinity for the norepinephrine uptake site of the norepinephrine transporter and the serotonin uptake site of the serotonin transporter, can be effectively employed as in Applicants' invention to prevent

or treat diseases and conditions such as attention deficit disorder, depression, obesity, Parkinson's disease and tic disorders.

The Office has previously acknowledged the novelty and nonobviousness of Applicants' compositions comprising a resolved (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane. In particular, Applicants' issued US Patent No. 6,569,887 B2, which claims (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane and compositions containing (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, was considered and issued by the Office over US Patent No. 4,118,417 disclosing the racemic mixture of the compound. The Office similarly considered and issued US Patent No. 6,716,868 B2 to Applicants claiming methods of treating or preventing disorders alleviated by inhibiting dopamine reuptake using (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane.

In view of the foregoing, Applicants respectfully submit that the Office has not established *prima facie* evidence that the instant claims are unpatentable over Beer et al., or, alternatively, that teachings of the instant disclosure, evincing usefulness of the (-) isomer within the presently-claimed methods, fail to establish "unexpected results" sufficient to overcome such *prima facie* evidence, if found. Therefore, the rejection of claims 22, 26-29, 31-44 and 49-52 under 35 USC § 103(a) as allegedly unpatentable over Beer et al., US 6,204,284 B1 is believed to be overcome.

Double Patenting

Claims 24, 26-29, 31-44 and 49-52 have been provisionally rejected under 35 U.S.C. 101 as allegedly claiming the same invention as that of Claims 25, 30 and 45-48 of copending Application No. 10/764,371. This rejection is respectfully submitted to be improper because, as noted above, the claims of Application No. 10/764,371 are directed to methods of treating addictive disorders while the claims of the present application are directed to methods of treating different diseases and conditions, that is, attention deficit disorder, depression, obesity, Parkinson's disease, and tic disorders. The claims of the present application are therefore not directed to the same invention as the claims of Application No. 10/764,371. Accordingly, this rejection should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at (425) 455-5575.

Dated this 3rd day of August, 2005.

Respectfully submitted,

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